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A Minimal Model Approach for the Description of Postprandial Glucose Responses from Glucose Sensor Data in Diabetes Mellitus

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Abstract—Modelling of the gluco-regulatory system in response to an oral glucose tolerance test (OGTT) has been the subject of research for decades. This paper presents an adaptation to the well-established oral minimal model that is identifiable from glucose data only and is able to capture the dynamics of glucose following both OGTT and mixed meal consumption. The model is in the form of low-dimensional differential equations with a recently introduced input function consisting of Gaussian shaped components. It was identified from glucose data recorded from six subjects without diabetes, prediabetes and type 2 diabetes under controlled conditions. The inferred parameters of the model are shown to have physiological meaning and produce realistic steady state behavior. This model may be useful in the development of clinical advisory tools for the treatment and prevention of non-insulin dependent type 2 diabetes mellitus.

I. INTRODUCTION

The measurement and subsequent analysis of blood glucose (BG) plays a central role in the diagnosis and treatment of type 2 diabetes mellitus (T2D) and is manifested by gradual degeneration of the body's ability to maintain the glucose concentration within a healthy range leading to hyperglycemia. Before the diagnostic criteria of T2D are fulfilled and symptoms of hyperglycemia become apparent, patients typically progress through asymptomatic stages of impaired glucose tolerance and/or impaired fasting glucose, referred to as prediabetes (PreD) [1].

The advent of cheap and reliable systems for continuous glucose monitoring (CGM) has made it possible to collect glucose data for up to 7 days and provided further insight into the various factors that influence BG levels, e.g. food, exercise and stress. Especially the responses to food has been shown to have high inter-personal variability [2], therefore calling for a highly personalized approach in the development of appropriate clinical treatment strategies.

There is a considerable amount of work focused on the modelling of the gluco-regulatory system in response to an oral glucose tolerance test, which involves the ingestion of 75 g of glucose after an overnight fast. The most commonly used approach to examine the body's response to the test involves the oral minimal model [3]. This method requires the simultaneous measurement of insulin concentrations, making it unsuitable for the widespread use in clinical practice. In this work we present a model-based approach for the assessment of OGTT responses under controlled conditions using CGM

data only. This has not been attempted yet and is accomplished by developing a modified version of the minimal model whose parameters can be identified from glucose data only. Additionally, the piecewise linear function used in the original model to describe the appearance of glucose [3] is replaced by novel input function recently introduced by our group [4]. It consists of two Gaussian shaped components and has been shown to provide a high degree of flexibility in the description of mixed meal glucose responses in healthy subjects in conjunction with a different model [4]. A further adaptation compared to the original model is the separate description of steady state and initial value of glucose concentration in order to account for the non-stationary behavior of glucose concentration [5] and a change in settling value over the course of the meal response.

In modelling of postprandial glucose profiles, the focus lies often on single responses [6, 7]. However this approach is unsuitable for the description of subsequent meal responses as it neglects the effects from previous meals by assuming the system is at steady state before meal consumption. In this work we overcome this assumption by describing subsequent responses within the same model, therefore incorporating the effects of past meals into the description of subsequent responses.

The capabilities of the modelling approach presented here will be demonstrated on real CGM data, collected from a highly diverse group of subjects at different stages of glucose tolerance. This approach of using of CGM data for model identification is emerging as a technique [6, 8, 9] and relieves the burden of acquiring additional, experimentally extensive signals such as insulin. Additionally it facilitates the development of personalized tools for clinical practice, where typically only glucose data is available and a variety of CGM systems are already in use [10].

II. METHODS

A. Data collection and study protocol

An experimental study involving six subjects (5 male, 1 female, Age: 44-61, BMI: 25.2-49.8 kg/m², HbA1c: 33-76 mmol/mol) undergoing inpatient monitoring was conducted at the Human Metabolism Research Unit at the University Hospitals Coventry and Warwickshire, UK. The cohort included two healthy, non-diabetic subjects, one subject with PreD and three subjects with non-insulin dependent T2D on

different combinations of oral anti-diabetic drugs. The prescribed drug regime was not altered during the course of the study. CGM data was collected using the Medtronic iPro2 CGM system (Medtronic MiniMed, Northridge CA, USA). Calibration was performed according to the manufactures instructions using capillary blood glucose concentrations, measured with the Abbott Freestyle Navigator 2 device (Abbot Diabetes Care Inc., Alameda CA, USA). The experiment lasted for 24 hours commencing at 19:00 on day one, approximately 2 days after CGM sensor insertion.

For this analysis glucose data collected between 08:15 and 18:45 on day two was considered. After an overnight fast, the subjects ate two meals: breakfast was consumed at 08:30 and consisted of a liquid meal containing 75 g of pure glucose, therefore simulating an OGTT. Lunch was consumed at 13:00 and consisted of a low carbohydrate mixed meal (20 % carbohydrates, 40 % fat, and 40 % protein, given as relative calorie content). Absolute amounts of carbohydrates, fat and protein in this meal were adapted for each subject to provide 40 % of estimated daily calorie demand and averaged to 51 g carbohydrate, 40 g fat and 91 g protein. At 17:30 subjects performed 30 min of moderate stepping exercise, before finishing the experiment at 18:45.

The experimental study involving human subjects received appropriate ethical approval from the National Research Ethics Service of the National Health Service (UK) including the compliance with the Ethical Principles for Medical Research on Human Subjects set by the Declaration of Helsinki (REC Reference: 17/NW0277).

B. Model formulation

In order to describe the response to a single meal in all subjects, we propose the following model:

$$\begin{aligned} \dot{G}(t) &= -G(t)X(t) - \theta_3[G(t) - G_b] + Ra(t) & G(0) &= G_0 \\ \dot{X}(t) &= -\theta_1 X(t) + \theta_2[G(t) - G_b] & X(0) &= 0 \end{aligned} \quad (1)$$

$$y(t) = G(t) + \varepsilon \quad \varepsilon \sim N(0, \lambda^2) \quad (2)$$

$$Ra(t) = H_1 \exp\left[-\frac{(t-T_1)^2}{w_1}\right] + H_2 \exp\left[-\frac{(t-T_2)^2}{w_2}\right] \quad (3)$$

$G(t)$ and G_0 represent the glucose concentration and its respective initial condition, $X(t)$ describes a general glucose lowering effect and $Ra(t)$ represents the rate of glucose appearance following meal consumption. In (2), $y(t)$ is the observed CGM data, and ε the measurement error modelled as Gaussian distributed white noise with zero mean and standard deviation λ . The system parameters governing the intrinsic model behavior are the rate parameters θ_1 to θ_3 and the basal value G_b , also representing the steady state of the system. The input function $Ra(t)$ in (1) is defined as the summation (3) of two Gaussian-shaped components [4]; parameters T_1 and T_2 correspond to the time of maximum height of each respective component; H_1 and H_2 to the height of these components; w_1 and w_2 to the respective squared widths. This means that we assume the presence of two, possibly overlapping, Gaussian components per meal. For the description of OGTT and mixed meal responses within the same model, two additional Gaussian components with parameters H_3, T_3, W_3 and H_4, T_4, W_4 were added to the input

function (3) and timing parameters (T_3 and T_4) can be adjusted according to the time of meal consumption.

The nonlinear model in (1) is based on the well-established oral minimal model of glucose kinetics [3]. In order to make the model identifiable from glucose data only, the second term in the description of $X(t)$ was introduced to represent a glucose dependent stimulus on $X(t)$, similar to the model in [8].

C. Parameter estimation and prior choice

For parameter estimation, a variational Bayesian numerical method was employed. This fully Bayesian approach [11] expresses parameters as probability distributions rather than fixed values and allows the use of existing information to specify prior distributions.

In this work, the entire process of parameter estimation was carried out in two main steps and repeated for each individual subject separately. In the first step, the time series was truncated just before the consumption of the mixed meal (lunch) and the parameters were estimated from the data of the OGTT response only. This means that the two Gaussian components describing the appearance of glucose from the mixed meal were initially removed. The following assumptions on prior distributions were made. Due to the lack of information, the parameters θ_1 to θ_3 were given flat prior distributions with large variances; the prior for G_b was based on the average between the first (measured just before the OGTT) and last points (just before consumption of the mixed meal) of the time series, respectively, with variance based on the measurement error of the CGM system [12]. The same information on measurement error was utilized for the prior distribution of the measurement uncertainty λ . The priors for the input function were again chosen to be rather flat with the exception of parameter T_1 , which was based on the time of meal consumption with a narrow distribution.

The second step of parameter inference utilized the full time series containing both OGTT and mixed meal responses until the start of the exercise period. Therefore the full model including all four Gaussian input function components was used. However, the system parameters (θ_1 to θ_3 and G_b) and the respective input function parameters (H_1, T_1, W_1 and H_2, T_2, W_2), inferred from the OGTT response were fixed. During subsequent model inversion with the time series from both responses, only the parameters governing the measurement uncertainty (λ) and mixed meal glucose appearance (H_3, T_3, W_3 and H_4, T_4, W_4) were updated. Here the priors were identical to step one with only the priors for T_3 and T_4 adjusted according to the time of mixed meal consumption.

D. Identifiability analysis

By utilizing software packages based on computing the rank of a numerically instantiated Jacobian matrix (observability/identifiability matrix) [13], the structural identifiability of the model was proven.

E. Assessment of model fit and steady state behavior

To assess the model fit, the root mean-squared error (RMSE) between model output and CGM data was calculated from the results of fitting both meals simultaneously.

In order to assess the steady state behavior of the model in conjunction with the inferred parameters, the model output was simulated further than the time duration covered by the given time series used for model inversion. Firstly, the output was simulated beyond the duration of the OGTT response for the case that no lunch would be consumed, i.e. H_3 and H_4 to be zero (see dotted line in Fig. 1 (a)-(c)).

Secondly the model output beyond the duration of the response from the mixed meal was simulated for the case that no exercise would be carried out (see solid line extending beyond the black crosses in Fig. 1 (a)-(c)).

F. Parameter interpretation

In order to facilitate the interpretation of the results from the parameter estimation process, the parameters describing the glucose appearance of OGTT and mixed meal were collated in the following quantities:

$$R_{AUC} = \frac{H_1\sqrt{W_1}+H_2\sqrt{W_2}}{H_3\sqrt{W_3}+H_4\sqrt{W_4}} \quad (4)$$

$$DT_{OGTT} = T_2 - T_1 \quad (5)$$

$$DT_{MM} = T_4 - T_3. \quad (6)$$

Equation (4) gives the ratio between the areas under the curves (AUC) of glucose appearance for OGTT and mixed meal, respectively, therefore describing the ratio between the amounts of glucose absorbed during the meals. Equations (5) and (6) describe the time difference between input function components, providing a measure for the duration of inferred glucose absorption.

III. RESULTS

A. Parameters

The inferred parameter means of the system parameters, and as well as quantities from (4)-(6) are displayed in Table I.

TABLE I. RESULTS OF PARAMETER ESTIMATION

| Parameters | Subjects | | | | | |
|---|-----------------------------|-----------------------------|--------------------------|-------------------------|-------------------------|-------------------------|
| | <i>S1</i> <i>Healthy</i> | <i>S2</i> <i>Healthy</i> | <i>S3</i> <i>PreD</i> | <i>S4</i> <i>T2D</i> | <i>S5</i> <i>T2D</i> | <i>S6</i> <i>T2D</i> |
| θ_1 [$10^{-2}/\text{min}$] | 1.93 | 2.97 | 1.62 | 0.07 | 17.77 | 58.14 |
| θ_2 [$10^{-4} \text{L}/(\text{mmol} \cdot \text{min}^2)$] | 2.65 | 3.37 | 0.68 | 0.16 | 0.47 | 0.54 |
| θ_3 [$10^{-2}/\text{min}$] | 2.60 | 3.85 | 0.13 | 0.50 | 0.88 | 1.85 |
| G_b [mmol/L] | 4.6 | 4.1 | 5.1 | 4.5 | 5.7 | 6.2 |
| R_{AUC} | 2.6 | 2.1 | 2.6 | 1.9 | 7.2 | 2.6 |
| DT_{OGTT} [min] | 66.2 | 55.2 | 53.6 | 119.2 | 46.0 | 65.2 |
| DT_{MM} [min] | 132.2 | 95.1 | 191.6 | 134.2 | 119.4 | 110.4 |
| RMSE [mmol/L] | 0.05 | 0.05 | 0.15 | 0.24 | 0.18 | 0.1 |

B. Model fit and steady state behavior

The RMSE results from the fitting of both meals are displayed in Table I and have a mean of 0.13 mmol/L. It is shown that they consistently lie below the measurement uncertainty of the CGM system of 0.8 mmol/L [12].

Examples of the collected data, model output and input function for three selected subjects are shown in Fig. 1 (a)-(c).

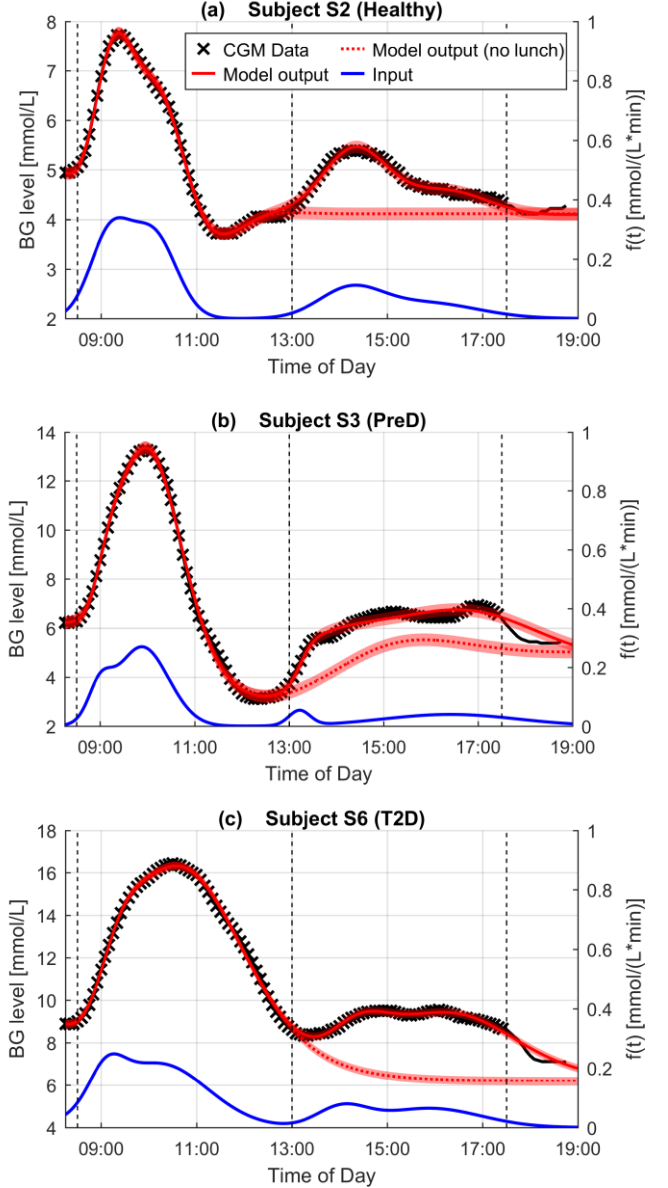


Fig. 1: Modelling results for (a) subject S2 without diabetes, (b) subject S3 with prediabetes and (c) subject S6 with T2D. The model output is displayed with respective uncertainty as shaded area. The solid black line extending beyond the CGM data points shows the subsequent glucose profile not used in the parameter inference process. The dashed black lines mark the beginnings of meal consumption and exercise. The dotted lines show the model response for the case that no lunch would be consumed, i.e. H_3 and H_4 to be zero.

IV. DISCUSSION

In this work, the well-established oral minimal model was adapted to be suitable for the identification from glucose data only, therefore avoiding the elaborate measurement of insulin concentrations. The RMSE values demonstrate that the model is capable of fitting OGTT responses from a heterogeneous subject population well and the subsequent model output is showing realistic steady state behavior. This means that the

model predicts physiologically valid settling values (G_b in Table I) with no unrealistic oscillations (Fig. 1 (a)-(c)). To the author's knowledge, this is the first time the model-based description of OGTT responses recorded with CGM has been attempted.

Additionally, the results demonstrate that an equally good fit can be achieved for a subsequent mixed meal with a very different composition and calorie content in comparison to the OGTT. A key factor in achieving this flexibility is the use of the specific input function described by expression (3). Compared with the piecewise linear function proposed in the original minimal model, function (3) is far more versatile despite having less parameters. The results also demonstrate that it is important to consider the response to the mixed meal following the OGTT, since a complete relaxation to the steady state, cannot be assumed, even four and a half hours after consumption (Fig. 1 (b) and (c)).

When analyzing the simulated model output beyond the mixed meal into the exercise period in Fig. 1 (b) and (c), it is shown that the settling time of glucose levels from measurements is decreased compared to model predictions. This again can be considered realistic behavior, as exercise is known to increase glucose uptake and reduce glucose output [14].

The results of the inferred model parameters allow the following observations. With the exception of subject S5, the ratios of AUCs of glucose appearance between OGTT and mixed meal (R_{AUC}) stay consistent across subjects. This suggests that the inferred total amount of absorbed glucose is independent of subject characteristics and only dependent on meal characteristics. It furthermore demonstrates that the total glucose appearance is significantly reduced during the mixed meal by a factor of R_{AUC} . Inspection of the time differences between input function components in OGTT and mixed meal glucose appearance reveals that DT_{MM} is consistently greater than DT_{OGTT} . These observations suggest that the addition of fat and protein prolongs the appearance of glucose in comparison to the OGTT. This could be caused by delayed gastric emptying [15] and therefore explains the reduction of glycemic exposure in mixed meals [16]. All these observations suggest realistic features, providing the basis for further investigations on the responses to a greater variety of meal compositions and more realistic scenarios, e.g. multiple meals in short succession.

The results of fitting the system parameters (θ_1 to θ_3 and G_b) demonstrate that the parameter θ_2 displays the most apparent and clear distinction between healthy subjects and subjects with T2D or prediabetes. This parameter governs the strength of coupling of $G(t)$ into the state of $X(t)$. As this state describes a general glucose lowering effect, the stronger increase of $X(t)$ in response to a rise in $G(t)$ above baseline in healthy subjects can be considered physiologically plausible. This could suggest that this parameter has a similar physiological interpretation as the insulin sensitivity, they key measure inferred from the original minimal model [3]. However this conjecture will be the subject of further investigations.

In terms of practical applications, we argue that due to its minimal requirements regarding data collection the model is

suitable to objectively assess, and subsequently prevent, postprandial hyperglycemia for a range of subjects with different stages of glycemic control. This could support the development of clinical advisory tools in the treatment and prevention of non-insulin dependent T2D.

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